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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/049,404
Filing Date: August 05, 2002
Appellant(s): ARNDT ET AL.

Steven J. Hultquist
Kelly K. Reynolds
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on March 23, 2007 appealing from the Office action mailed on August 24, 2006.

The text of those Sections of Title 35 U.S. Code not included in this Appeal can be found in a previous Office Action herein.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

(A) Hartmann et al. "Treatment of refractory Hodgkin's Disease with an anti-CD16/CD30 bispecific antibody" Blood, Vol.89 (1997), pp.2042-2047.

(B) Hartmann et al. "Anti-CD16/CD30 bispecific antibodies as possible treatment for refractory Hodgkin's disease" Leukemia and Lymphoma, Vol.31 (1998), pp.385-392.

(C) Holliger et al. "Diabodies: small bivalent and bispecifc antibody fragment" Proc. Natl. Acad. Sci. USA, Vol.90 (1993), pp.6444-6448.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection under 35 U.S.C. 112, second paragraph

Claim 22 stands rejected under **35 U.S.C. 112, second paragraph,** as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

Claim 22 is indefinite in the recitation of "a more intense lysis" because "a more intense lysis" is a relative phrase which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Rejection under 35 U.S.C. 112, first paragraph

Claim 22 stands rejected under **35 U.S.C. 112, first paragraph,** as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the antibody bimAbHRS-3/A9 (DSM ACC2124) is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

It is noted that appellant has indicated that the antibody bimAbHRS-3/A9 (DSM ACC2124) was described in US Patent 5,643,795 (see page 2 of the amended specification).

However, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that appellant and other members of the public were able to obtain the materials in question from a given depository prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public. Appellant did not make of record any of the facts and circumstances surrounding the access to the biological materials from the depository, nor is there any evidence as to the depository's policy regarding the material if a patent would be granted. Further, there is no assurance that the depository would allow unlimited access to the material if the application has matured into a patent. In the absence of evidence that the antibody bimAbHRS-3/A9 (DSM ACC2124) is readily available to the public and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the rejection under enablement requirements of 35 USC 112, first paragraph, is set forth herein.

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by appellants or someone with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, appellant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the appellant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Rejection under 35 U.S.C. 102(b)

Claims 1-5, and 15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hartmann et al. (Blood. 1997, 89;6:2042-2047).

Hartmann et al. teach an anti-CD16/CD30 bispecific antibody binds one arm to CD30, which is expressed on Hodgkin, and Reed-Sternberg cells and its second arm binds to CD16 on NK cells and is able to induce specific lysis of CD30 positive tumor cells (see entire document, particularly page 2042). Hartmann et al. further teach that the side effects such as HAMAs in the anti-CD16/CD30 bispecific antibody treatment can be resolved by using less immunogenic bispecific single chain antibody or diabodies (e.g. see page 2046 in particular).

Although the references does not disclose "encoded by expression vector pKID16-30" (see instant claim 5), it is noted that the reference teaches an anti-CD16/CD30 bispecific antibody that appears to be the same as, or an obvious variant of, the product set forth in the product-by-process claim 5 although produced by a different process. See In re Marosi, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). See also MPEP 2113. Therefore, claim 5 has been included in this rejection.

Therefore, the reference teachings anticipate the claimed invention.

Rejection under 35 U.S.C. 103(a)

Claims 1-6, 15 19, and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hartmann et al (Leukemia and Lymphoma. 1998, 31:385-392. Reference AG on IDS) in view of Holliger et al. (Proc. Natl. Acad. Sci. USA, Vol.90 (1993), pp.6444-6448).

Hartmann et al. teach that anti-CD16/CD30 bispecific antibody, HRS-3/A9, binds with one arm to CD30 expressed on Hodgkin and Reed-Sternberg cells and with its second arm binds CD16 on NK cells leading to specific tumor cell killing (see entire document, particularly Introduction on pages 385-386). Hartmann et al. further teach that said bispecific antibody can induce a regression of Hodgkin's disease in patients (see second paragraph on the right column of page 390).

Hartmann et al. does not teach an anti-CD16/CD30 Fv construct with peptide linkers joining a VH domain of an anti-CD16 antibody and a VL domain of an anti-CD30 antibody and a VH domain of an anti-CD30 antibody and a VL domain of an anti-CD16 antibody, wherein the Fv construct does not have constant domains.

However, methods of making Fv or diabodies that have the same antigen specificity but without Fc region were well known in the art at the time the invention was made. For example, Holliger et al. teach methods of making small bivalent and bispecific antibody fragments by linking the V_H and V_L of any two different antibodies A and B to form two different "cross-over" chains V_HA-V_LB and V_HB-V_LA via peptide linkers (see entire document, particularly first paragraph on the left column of page 6446).

Holliger et al. further teach that the binding affinity of the bivalent and bispecific diabodies have improved affinity to its antigens (see Table 2 on page 6447 and paragraph 3 on the right column of page 6446, in particular).

Furthermore, Holliger et al. teach that antibody fragment are preferable to whole antibodies because the Fc region of antibodies can lead to illegitimate targeting to cells expressing Fc receptors (e.g. see lines 9-10 on the left column of page 6444). Further diabodies are smaller in size than whole antibody and can facilitate penetration of tumors (e.g. see last paragraph on the left column of page 6448).

It would have been obvious to the ordinary artisan at the time the invention was made to make an antiCD16/CD30 Fv construct with peptide linkers joining a VH domain of an anti-CD16 antibody and a VL domain of an anti-CD30 antibody and a VH domain of an anti-CD30 antibody and a VL domain of an anti-CD16 antibody, wherein the Fv construct does not have constant domains. The ordinary artisan would have been motivated to produce the Fv construct in particular for treating human Hodgkin's lymphoma because bispecific anti-CD16/CD30 antibody HRS-A9 can be used to treat Hodgkin's lymphoma and it was well known in the art that Fv construct is beneficial over whole antibody in that it can avoid illegitimate targeting to cells expressing Fc receptors (e.g. see lines 9-10 on the left column of page 6444) and can facilitate tumor penetration (e.g. see last paragraph on the left column of page 6448).

Regarding the claimed limitation of "capable of inducing a more intense lysis of CD30 carrying cells in vitro than bimAbHRS-A9", given that Holliger et al. teach that the binding affinity of the bivalent and bispecific diabodies have improved affinity to its antigens; one of ordinary skill in the art would at once envisage or had reasonable expectation of success that the Fv construct having variable domains for CD16 and a CD30 but no constant domains would be able to induce more intense lysis of CD30 carrying cells in vitro than the bispecific anti-CD16/CD30 antibody HRS-3/A9 due to increased antigen affinity.

Although the references does not disclose "encoded by expression vector pKID16-30", per se (see instant claim 5), it is noted that references teach an anti-CD16/CD30 bispecific antibody that appears to be the same as, or an obvious variant of, the product set forth in the product-by-process claim 5 although produced by a different process. See *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). See also MPEP 2113. Further, it is noted that products of identical chemical composition can not have mutually exclusive properties; a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, claim 5 has been included in this rejection.

Giving the teachings of Hartmann et al. regarding the effect of bispecific antiCD16/CD30 antibody in treating Hodgkin's lymphoma, and the teachings of Holliger et al. providing methods of making small bivalent and bispecific antibody fragments by linking the V_H and V_L of any two different antibodies A and B to form two different "cross-over" chains V_HA-V_LB and V_HB-V_LA via peptide linkers, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing an anti-CD16/CD30 Fv construct with peptide linkers joining a VH domain of an anti-CD16 antibody and a VL domain of an anti-CD30 antibody and a VH domain of an anti-CD30 antibody and a VL domain of an anti-CD16 antibody, wherein the Fv construct does not have constant domains.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Rejection under 35 U.S.C. 112, second paragraph

Appellant's arguments have been fully considered but have not been found convincing.

(A)) Definition of the term in the claim

Appellant argues that claim 22 recites "inducing a more intense lysis of CD30 carrying cells in vitro than bimAbHRS-3/A9 (DSM ACC 2142)"; thus, appellant argues that the term "more lysis" is defined by the claim.

This is not found persuasive for following reasons:

The term "a more intense lysis" is a relative phrase which renders the claim indefinite. Further, even though the claim recites "inducing a more intense lysis of CD30 carrying cells in vitro than bimAbHRS-3/A9 (DSM ACC 2142)", CD 30 carrying cells are either lysed or not lysed; it is not clear how CD30 carrying cells can be *lysed more intensely*. Thus, the metes and bounds of the phrase is unclear and ambiguous.

(B) Definition of the term in the specification and reasonable apprised of one of skill in the art

Appellant argues that the comparison of the lysis of CD30 cells in vitro induced by the Fv construct and by bispecific anti-CD16/CD30 bimAbHRS-3/A9 antibody was disclosed in Example 3(B) which displayed a JAM cytotoxicity test using the said Fv construct and said bispecific antibody.

This is not found persuasive for following reasons:

Contrary to appellant's assertion, it is noted that neither the Fv construct nor the bispecific anti-CD16/CD30 bimAbHRS-3/A9 antibody is capable of inducing lysis of CD30 carrying cells.; rather, the Fv construct and the bispecific antibody bridge effector cells such as natural killer cells (NK cells) to tumor cells and the lysis of tumor cells are mediated through activation of the NK cells (see second paragraph on page 1 of the instant specification).

Regarding Example 3(B) on pages 9-10 of the instant specification and Figure 3, it is not clear how the Fv construct is compared to the bispecific antibody in the cytotoxicity assays; for example, the specification has not taken in to consideration that the Fv construct has no Fc region, thus the Fv construct is a smaller molecule than antibody bimAbHRS-3/A9. For example, 1 ug/ml of the Fv would contain more antigen binding fragments than the antibody bimAbHRS-3/A9 in equal amount and 1ug/ml Fv construct would be expected to have more effect in recruiting NK cells than 1 ug/ml full antibody. Therefore, the specification fails to provide appropriate control and side-by-side testing to the claimed limitation of *"inducing a more intense lysis of CD30 carrying cells in vitro than bimAbHRS-3/A9 (DSM ACC 2142)"*.

Therefore, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Rejection under 35 U.S.C. 112, first paragraph

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant further argues that the antibody bimAbHRS-3/A9 is the subject matter of US Patent 5,643,759 and that said antibody has been deposited under Budapest Treaty on August 6, 1993 to the DSM depository as DSM ACC 2142 and is freely accessible to the public; thus appellant argues that the antibody bimAbHRS-3/A9 is available to the public until 2023, 30 years from the date of the deposit.

This is not found persuasive for following reasons:

The examiner agrees with appellant that the antibody bimAbHRS-3/A9 (DSM ACC2124) was described in US Patent 5,643,795 (see page 2 of the instant amended specification).

However, it is noted that the US Patent 5,643,759, for which appellant is relying on to satisfy all of the deposit requirement under 35 U.S.C. 112, first paragraph, *has expired due to nonpayment of maintenance fees under 37 C.F.R. 1.362.*

Given the expiration of the US Patent 5,643,759 relied upon by appellant to satisfy the deposit requirement of the claimed antibody bimAbHRS-3/A9 (DSM ACC2124), there are no assurances that those entities in control of the claimed antibody bimAbHRS-3/A9 (DSM ACC 2142) would allow unlimited access to the antibody if the instant appliciation would mature into a patent, consistent with the requirement for the deposit of biological material under 35 U.S.C. 112, first paragraph, enablement and the deposit rules under 37 C.F.R. 1.801-1.809. Also see MPEP 2404.01.

Rejection under 35 U.S.C. 102(b)

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant does not dispute that Hartmann et al. (Blood. 1997, 89;6:2042-2047) teach Fv or diabodies.

However, appellant argues that Hartmann et al. only provide general discussion of the Fv and diabodies thus the reference only teach the genus of diabodies and would not anticipate the claimed species of anti-CD16/CD30 Fv antibody construct.

This is not found persuasive for following reasons:

In contrast to appellant's assertion that the reference merely teach a genus of Fv or diabodies, it is noted that the teachings of the reference is centered in the use of anti-CD16/CD30 bispecific antibody in treating human patients suffering from Hodgkin's lymphoma (e.g. see title and Page 2042 in particular). Hartmann et al. (Blood. 1997, 89;6:2042-2047) clearly teach that the side effects such as HAMAs in the anti-CD16/CD30 bispecific antibody treatment can be resolved by using less immunogenic bispecific single chain antibody or diabodies (see entire document, particularly pages 2042-2046).

Therefore, the teachings of Fv and diabodies by Hartmann et al. are within the content of improvement over anti-CD16/CD30 bispecific antibody in treating Hodgkin's lymphoma, thus, are not generic of any Fv or diabodies but rather, Fv and diabodies with specific binding to CD16 and CD30 antigen.

Further, it is noted that a generic chemical formula will anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). Also see MPEP 2131.02.

In this case, even if Hartmann et al. teach a genus of Fv and diabodies, one of ordinary skill in the art would at once envisage the structure of the claimed Fv antibody construct having variable domain for CD16 and a CD30 but no antibody constant domains and including a regression of Hodgkin's disease in vivo.

Rejection under 35 U.S.C. 103(a)

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant argues that Hartmann et al. (Leukemia and Lymphoma. 1998, 31:385-392) do not teach or suggest any other antibody format except for the bispecific anti-CD16/CD30 IgG antibody. Appellant further argues that Holliger et al. do not teach suggest a bispecific Fv construct that is capable of inducing a regression of Hodgkin's disease in vivo nor does Holliger et al. show any cytotoxic activity of the Fv constructs. Thus, appellant argues that one of skill in the art would not have been motivated to combine the teachings of the two references.

This is not found persuasive for following reasons:

In response to appellant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

Regarding the reasons of combining the teachings of Hartmann et al. and Holliger et al., it is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In this case, Hartmann et al. teach bispecific anti-CD16/CD30 antibody HRS-3/A9 can be used for immunotherapy for tumor-specific recruitment and activation of immunologic effector cells (see entire document, particularly pages 385-390). Hartmann et al. further teach that the bispecific anti-CD16/CD30 antibody HRS-3/A9 is a murine IgG1 antibody (e.g. see lines 7-10 on the left column of page 386) and can induce side effect of human anti-mouse immunoglobulin antibodies (HAMA) (see second paragraph on the right column of page 390, in particular) and suggest treatment options of using small bivalent and bispecific antibody fragments and refer to reference 25 that teach such small bivalent and bispecific antibody fragments (see last three lines on the left column of page 391 and note that reference 25 referred by Hartmann et al. is Holliger et al, see [25] on page 392).

Further, contrary to appellant's assertion that Holliger et al. do not teach cytotoxic Fv antibody, it is noted that Holliger et al. clearly teach that diabodies represent a class of bivalent and bispedific antibody fragments similar in size to a Fab fragment and can facilitate penetration of tumors (e.g. see second paragraph on the left column of page 6448).

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Here, given that antigen binding fragments can be preferable to complete antibodies because the Fc region of antibodies can lead to unwanted targeting to cells expressing Fc receptors and that the bispecific anti-CD16/CD30 antibody binds CD30 expressed on Hodgkin and Reed-Sternberg cells and CD16 on NK cells leading to specific tumor cell killing, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of the references to reduce or eliminate the side effects associated with non-specific binding between the Fc region of bi-specific anti-CD16/CD30 antibody to the Fc receptors and thereby increasing efficacy.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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